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**Description/Abstract:**

Both animal and plant tissue exhibit a nonlinear rheological phenomenon known as compression stiffening, or an increase in moduli with increasing uniaxial compressive strain. Does such a phenomenon exist in single cells, which are the building blocks of tissues? One expects an individual cell to compression soften since the semiflexible biopolymer-based cytoskeletal network maintains the mechanical integrity of the cell and in vitro semiflexible biopolymer networks typically compression soften. To the contrary, we find that mouse embryonic fibroblasts (mEFs) compression stiffen under uniaxial compression via atomic force microscopy studies. To understand this finding, we uncover several potential mechanisms for compression stiffening. First, we study a single semiflexible polymer loop modeling the actomyosin cortex enclosing a viscous medium modeled as an incompressible fluid. Second, we study a two-dimensional semiflexible polymer/fiber network interspersed with area-conserving loops, which are a proxy for vesicles and fluid-based organelles. Third, we study two-dimensional fiber networks with angular-constraining crosslinks, i.e. semiflexible loops on the mesh scale. In the latter two cases, the loops act as geometric constraints on the fiber network to help stiffen it via increased angular interactions. We find that the single semiflexible polymer loop model agrees well with the experimental cell compression stiffening finding until approximately 35% compressive strain after which bulk fiber network effects may contribute. We also find for the fiber network with area-conserving loops model that the stress–strain curves are sensitive to the packing fraction and size distribution of the area-conserving loops, thereby creating a mechanical fingerprint across different cell types. Finally, we make comparisons between this model and experiments on fibrin networks interlaced with beads as well as discuss implications for single cell compression stiffening at the tissue scale.